REMARKS

Reconsideration of the present Application is respectfully requested in view of the above Amendments and the following Remarks. Claims 1-12, 14-19, 21-16, and 31-36 are currently under examination in this Application. Without acquiescence to any rejection, Applicants have amended claims 1, 24, 31, and 32 to point out with greater particularity and distinctly claim certain embodiments of Applicants' invention. No new matter has been added by these amendments. Support for the amendments can be found in the specification as originally filed, for example, on page 12, line 30 through page 13, line 4; page 18, lines 3-4; page 19, lines 25-27; page 39, lines 3-4; and Figure 22.

Rejections Under 35 U.S.C. § 112, First Paragraph, New Matter

The Examiner rejected claims 1-12, 14-19, 21-26, and 31-36 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner acknowledges that the specification describes a marrow stromal cell (MSC) plating method that generates x-fold expansion, but asserts that it does not describe a plating method that specifically teaches that plating cells at an initial density of less than about 50 cells per square centimeter results in a greater number of cells than when cells are plated at an initial density of more than about 50 cells per square centimeter (*see,* the Action, page 6). The Examiner therefore asserts that the amended claims add new matter to the specification.

Applicants respectfully traverse this rejection and submit the specification as filed reasonably conveys to a person skilled in the art that Applicants had possession of the claimed embodiments at the time of filing. Amendments to an application which are supported in the original description are *not* new matter. M.P.E.P. § 2163.07.

As previously made of record, the specification supports claim recitations relating to methods of plating and replating MSCs at an initial density of less than about 50 cells per square centimeter of growth surface wherein the method results in a greater total number of cells to be obtained compared to the total number of cells obtained from plating and replating at an initial density of more than about 50 cells per square centimeter of growth surface. As one example, Figure 11 in the specification depicts the expandability of MSCs from a 20ml bone

aspirate, in which plating MSCs at 3 cells/cm^2 (*i.e.,* less than about 50 cells/cm^2) greatly increases the number of cells to be obtained relative to plating MSCs at 5000 cells/cm^2 (*i.e.,* more than about 50 cells/cm^2) (*see, e.g.,* page 10, lines 25-27; page 39, lines 8-10; and Figure 11 of the specification). Specifically, Figure 11 describes a multiple log increase in the total number of cells to be obtained over 20-30 days in culture.

The specification also contrasts the improvements provided by culturing MSCs at an initial plating density of less than about 50 cells/cm^2 with prior art methods plating at an initial higher density (*i.e.,* a density higher than less than about 50 cells/cm^2) (*see, e.g.,* page 14, lines 9-18). A person skilled in the art would understand the equivalence between (i) plating cells at a higher density and (ii) plating cells at an initial density of more than about 50 cells/cm^2, as recited in the claims. Applicants submit that the specification as filed supports the claim recitations as amended.

If the Examiner's rejection under 35 U.S.C. § 112 is based in part on the assertion that the specification does not specifically teach by way of example that 50 cells/cm^2 is a critical density, then Applicants respectfully disagree with the Examiner's application of the written description standard. The written description requires neither (i) examples nor (ii) reduction to practice. *Falko-Gunter Falkner v. Inglis,* 448 F.3d 1357, 1366 (Fed. Cir. 2006) ("A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples covering the full scope of the claim language.") ("An actual reduction to practice is not required for written description."). The specification therefore need not provide specific, exemplary guidance (*i.e.,* an experimentation reduced to practice) as to whether 50 cells/cm^2 is a precise, critical density at which MSCs should be plated to generate enhanced expandability. Rather, as noted herein, the specification conveys to a person skilled in the art that Applicants had possession of a method in which a greater number of cells can be obtained by plating and replating cells at less than about 50 cells/cm^2 compared to plating and replating cells at more than about 50 cells/cm^2.

Nonetheless, without acquiescence to any rejection and merely to further prosecution of the claims, Applicants have amended claims 1, 24, 31, and 32. Embodiments of the amended claims are directed, in pertinent part, to methods of inducing or enhancing

proliferation of isolated human MSCs in vitro by plating and replating the cells at an initial density of less than about 50 cells/cm^2 of growth surface wherein the method generates enhanced expandability of marrow stromal cells relative to plating and replating at an initial density of more than about 50 cells/cm^2 of growth surface. Support for the amendment can be found throughout the specification. For example, the specification describes "enhanced expandability of MSCs generated" using the methods recited in the claims (*see, e.g.,* page 39, lines 3-4), and describes that the expansion of MSCs is improved "relative to" prior art expansion methods, which methods include plating cells at initial densities higher than about 50 cells/cm^2 (*see, e.g.,* page 19, lines 25-27).

The specification also describes "expandability" as the capacity of MSCs to proliferate or undergo population doublings (*see, e.g.,* page 18, lines 3-4). Figure 22 depicts the number of population doublings obtained when cells were plated and replated at low density (*i.e.,* 1.5 cells/cm^2, or less than about 50 cells/cm^2) as compared to being plated and replated at high density (*i.e.,* 5000 cells/cm^2, or more than about 50 cells/cm^2) (*see, e.g.,* page 12, line 30 through page 13, line 4; and Figure 22). As recited in the claims, this figure clearly describes how low density plating of MSCs generates enhanced expandability relative to high density plating, in that the number of population doublings continues to increase over time for cells plated and replated at less than about 50 cells/cm^2, whereas the number of population doublings plateaus for cells plated and replated at more than about 50 cells/cm^2. This description reasonably conveys to a person skilled in the art that Applicants possessed a method in which plating and replating cells at less than about 50 cells/cm^2 generates enhanced expandability of MSCs relative to plating and replating cells at more than about 50 cells/cm^2.

Applicants note that to comply with the written description requirement, the claims need not state, *in ipsis verbis*, the language found in the specification. Mere rephrasing of a passage does not constitute new matter, and rewording of a passage, so long as the same meaning remains intact, is permissible. (*See In re Anderson*, 471 F.2d 1237 (CCPA 1973), cited in M.P.E.P. § 2163.07). A person skilled in the art would understand from the original disclosure that permissible rephrasing of the claims has not added any new matter to the application.

Applicants submit that the specification as originally filed supports claims 1-12, 14-19, 21-26, and 31-36 as amended and therefore satisfies the written description requirement under 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request reconsideration and withdrawal of the new matter rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

The Examiner rejected claims 1-12, 14-19, 21-23, 25, 26, and 31-36 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. The Examiner asserts that the teachings in the post-filing reference, Sekiya *et al.* (*Stem Cells*, 2002, 20:530-541), are contrary to the claimed subject matter.

Applicants traverse this rejection and submit that the guidance provided in the specification enables a person skilled in the art to *make* and *use* the claimed subject matter without undue experimentation. In particular, Applicants respectfully disagree with the Examiner's application of Sekiya *et al.* as it relates to the instant claims.

In general, the Examiner should not use post-filing date references to demonstrate that the patent is non-enabling (*see* M.P.E.P. § 2164.05(a)), unless a person skilled in the art states that a particular invention is not possible years after the filing date. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993). Sekiya *et al.* in no way provide evidence that it is impossible to practice the subject matter of the instant claims. Rather, a closer look at the cited reference reveals that it is incomplete in certain respects, whereas in others it is entirely consistent with the subject matter of the instant claims.

The Examiner relies too heavily on the limited observation that "when MSCs are plated at 1000 cells per square centimeter, about 1.6 million cells obtained after 12 days in culture; cells plated at 10 cells per square centimeter yield 0.3 million cells" (*see* the Action, page 8). As one example of this undue reliance, Sekiya *et al.* merely report these results from a single experiment, using a single donor, in which the donor cells are noted expressly to be "less sensitive to plating density than cells from other samples" (*see, e.g.,* Sekiya *et al.*, page 533, column two, last sentence of carryover paragraph). Also, in contrast to Sekiya *et al.*, the instant specification teaches that plating MSCs at low initial density greatly increases the number of

cells to be obtained relative to plating MSCs at high initial density (*see, e.g.,* page 10, lines 25-27; page 39, lines 8-10; and Figure 11). A person skilled in the art would never understand that it is impossible to practice the presently claimed subject matter based on a single experiment with allegedly different results.

Moreover, the culture methods described in Sekiya *et al.* are significantly different than those presently claimed. Specifically, Sekiya *et al.* fail to perform replating of their culture cells, as recited in the instant claims. Embodiments of the instant claims relate to methods of plating and replating MSCs at initial lower cell densities to increase cell yield as compared to plating and replating at initial higher densities. The failure of Sekiya *et al.* to both plate and replate MSCs indicates to a person skilled in the art that the results reported in this reference are irrelevant to determining whether it is possible to practice the subject matter of the instant claims.

Nonetheless, without acquiescence to any rejection and merely to further prosecution of the claims, Applicants have amended claims 1, 31, and 32. Embodiments of the amended claims are directed, in pertinent pert, to methods of inducing or enhancing proliferation of isolated human MSCs *in vitro* by plating and replating the cells at an initial density of less than about 50 cells/cm^2 of growth surface wherein the method generates enhanced expandability of marrow stromal cells relative to plating and replating at an initial density of more than about 50 cells/cm^2 of growth surface.

Consistent with the purpose of the enablement requirement, the present application teaches a person skilled in the art how to *make* and *use* the claimed subject matter without undue experimentation. For example, the specification teaches that "expandability" of MSCs refers the capacity to proliferate or undergo population doublings (*see, e.g.,* page 18, lines 3-4). The specification also teaches that expandability of MSCs can be accurately correlated with their ability to form colonies in culture (*see, e.g.,* page 27, lines 1-3), and provides routine, exemplary methods for assessing colony-forming efficiency (*see, e.g.,* page 27, lines 12-16).

From the guidance provided in the specification, a person skilled in the art can culture MSCs (*see, e.g.,* page 29, line 9 through page 30, line 4), plate and replate MSCs at the appropriate initial cell density as disclosed in the specification and recited in the claims (*see, e.g.,*

page 6, line 31 through page 7, line 19; and claim 1), and determine, as described above, whether the claimed methods generate enhanced MSC expandability. A person skilled in the art can perform these routine experiments, and therefore make and use claimed embodiments, without undue experimentation.

Applicants submit that claims 1-12, 14-19, 21-23, 25, 26, and 31-36 satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. Applicants, therefore, respectfully request reconsideration and withdrawal of the enablement rejection, in view of the above amendments and remarks.

Rejections Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

The Examiner rejected claim 1 and those dependent therefrom, in addition to claim 24, under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. The Examiner asserts that claim 1 is unclear in using the recitation "50 cells per square centimeter of growth *factor*," and that claim 24 lacks antecedent basis for the recitation "the proliferated isolated marrow stromal cells."

Applicants traverse these grounds for rejection and submit that the claims as amended are clear. Claim 1 has been amended to recite "50 cells per square centimeter of growth *surface*," obviating the Examiner's rejection of claim 1 and those dependent therefrom.

Regarding claim 24, Applicants note that inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface. *See Bose Corp. v. JBL, Inc.*, 274 F.3d 1354, 1359 (Fed. Cir. 2001) (holding that recitation of "an ellipse" provided antecedent basis for "an ellipse having a major diameter" because "[t]here can be no dispute that mathematically an inherent characteristic of an ellipse is a major diameter"). Likewise, "the *proliferated* isolated marrow stromal cells" are an inherent component of isolated human MSCs *growing* on a surface in the presence of a growth medium. This inherent component (*i.e.*, proliferated), therefore, arguably has proper antecedent basis in the earlier recitation of the component itself (*i.e.*, MSCs growing).

Nonetheless, and without acquiescence to any rejection, claim 24 has been amended to recite, "whereby the isolated human marrow stromal cells proliferate," providing explicit antecedent basis for the recitation "the proliferated isolated marrow stromal cells." The present amendment obviates the Examiner's rejection of claim 24.

Applicants submit that claim 1 and those dependent therefrom, in addition to claim 24, are definite under the requirements of 35 U.S.C. § 112, second paragraph, and respectfully request reconsideration and withdrawal of this rejection in view of the above remarks and amendments.

Applicants respectfully submit that all claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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